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(54) Titre : AMIDES D'ACIDE ANTHRANILIQUE ET LEUR UTILISATION COMME MEDICAMENT
(54) Title: ANTHRANILIC ACID AMIDES AND THE USE THEREOF AS MEDICAMENTS

(57) Abrégé/Abstract:

The invention relates to anthranilic acid amides and the use thereof as medicaments for the treatment of diseases that are triggered by persistent angiogenesis, in addition to intermediate products in the production of anthranilic acid amides.

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ABSTRACT

The invention relates to anthranilic acid amides and the use thereof as medicaments for the treatment of diseases that are triggered by persistent angiogenesis, in addition to intermediate products in the production of anthranilic acid amides.

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EP 009908478

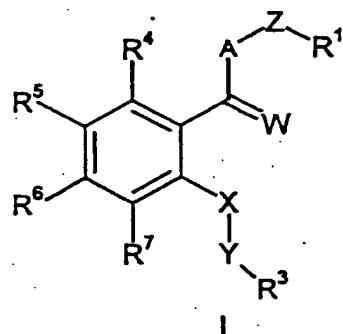
European Patent Office

GD1- Berlin Office

November 3, 2000

Claims

1. Compounds of general formula I

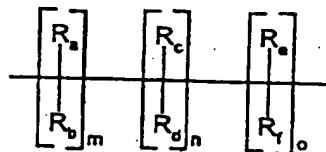


in which

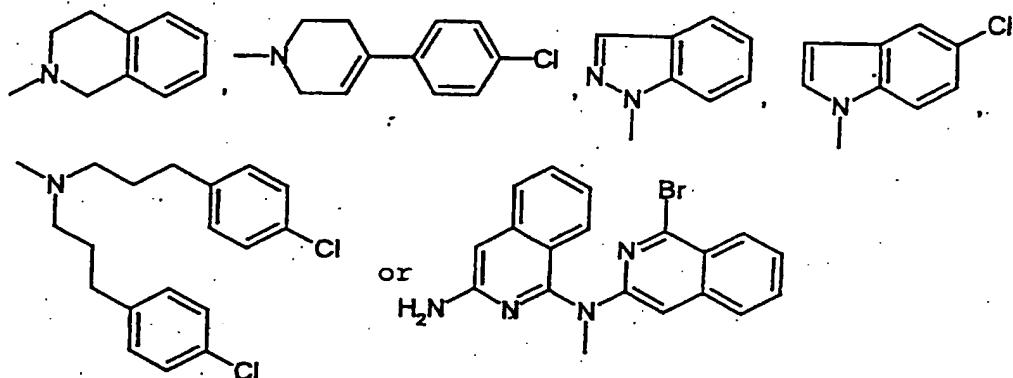
A stands for the group $=NR^2$,

W stands for oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,

Z stands for the group $=NR^{10}$, $=N-$, or $-N(R^{10})-(CH_2)_q-$, branched or unbranched C_{1-6} alkyl or the group

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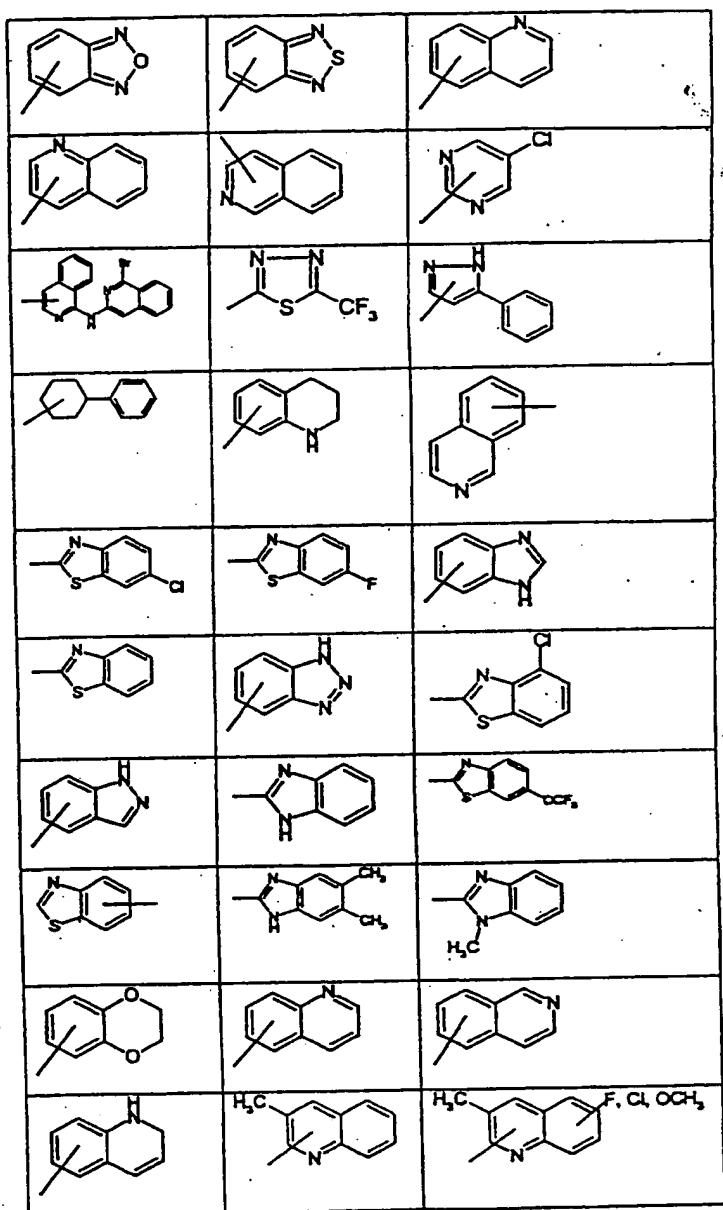
or A, Z and R¹ together form the group



m, n and o stand for 0-3,
 q stands for 1-6,
 R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen, C₁₋₄ alkyl or the group =NR¹⁰, and/or R_a and/or R_b can form a bond with R_c and/or R_d or R_c can form a bond with R_e and/or R_f,
 X stands for the group =NR⁹,
 Y stands for the group -(CH₂)_p,
 p stands for 1-4,
 R¹ stands for C₁₋₆ alkyl that is unsubstituted or is optionally

substituted in one or more places with halogen, C₁₋₆ alkyl, C₁₋₄ alkoxy, hydroxy, nitro, cyano or substituted in one or more places with halogen, or C₁₋₆-alkoxy-substituted naphthyl, biphenyl, phenyl, thiophenyl, furanyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl or isoquinolinyl; or 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl, or for the group

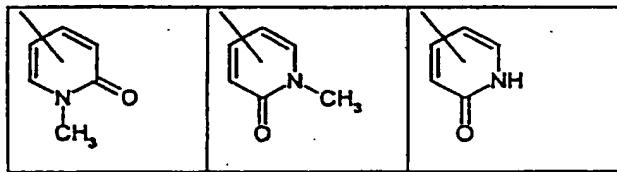
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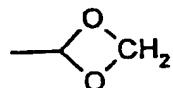
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whereby phenyl, substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or C_{1-6} alkyl,
 R^3 stands for naphthyl, biphenyl, phenyl, thiophenyl, furanyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl or isoquinolinyl that is unsubstituted or optionally substituted in one or more places with halogen, C_{1-6} alkyl, C_{1-6} alkoxy or hydroxy, or for the group



R^4 , R^5 , R^6 , and R^7 , independently of one another, stand for hydrogen, halogen, or C_{1-6} alkoxy, C_{1-6} alkyl or C_{1-6} carboxylalkyl that is unsubstituted or optionally substituted in one or more places with halogen,
or R^5 and R^6 together form the group



R^8 , R^9 , and R^{10} , independently of one another, stand for hydrogen or C_{1-6} alkyl,

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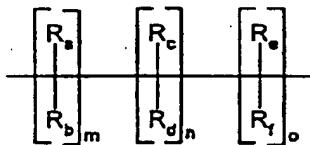
as well as their isomers and salts,

whereby

- a) If R^9 stands for hydrogen, Y stands for the group $-(CH_2)_p$, in which $p = 1$, R^3 stands for phenyl and W stands for oxygen, R^1 must not stand for unsubstituted imidazol-1-yl, and
- b) If W stands for oxygen, R^2 stands for hydrogen, R^9 stands for hydrogen,
 Y stands for the group $-(CH_2)_p$, in which $p = 1-4$ and R^1 stands for pyridyl,
 or
 Y stands for the group $-(CH_2)_p$, in which $p = 1$, and R^1 stands for phenyl or phenyl that is substituted in one place by methyl, chlorine or bromine, and Z stands for methyl or ethyl, R^3 must not stand for pyridyl, phenyl or phenyl that is substituted in one place by methyl, chlorine or bromine.

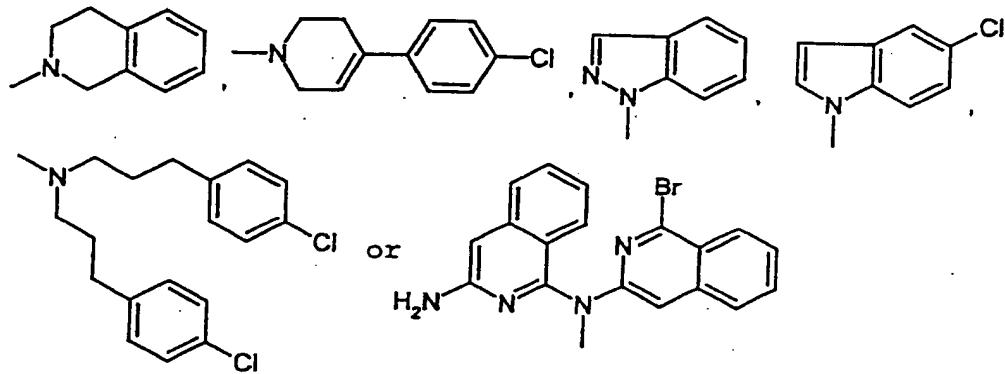
2. Compounds of general formula I, according to claim 1, in which

- A stands for the group $=NR^2$,
- W stands for oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,
- Z stands for the group $=NR^{10}$, $=N-$ or $-N(R^{10})-(CH_2)_q$, branched or unbranched C_{1-6} alkyl or the group



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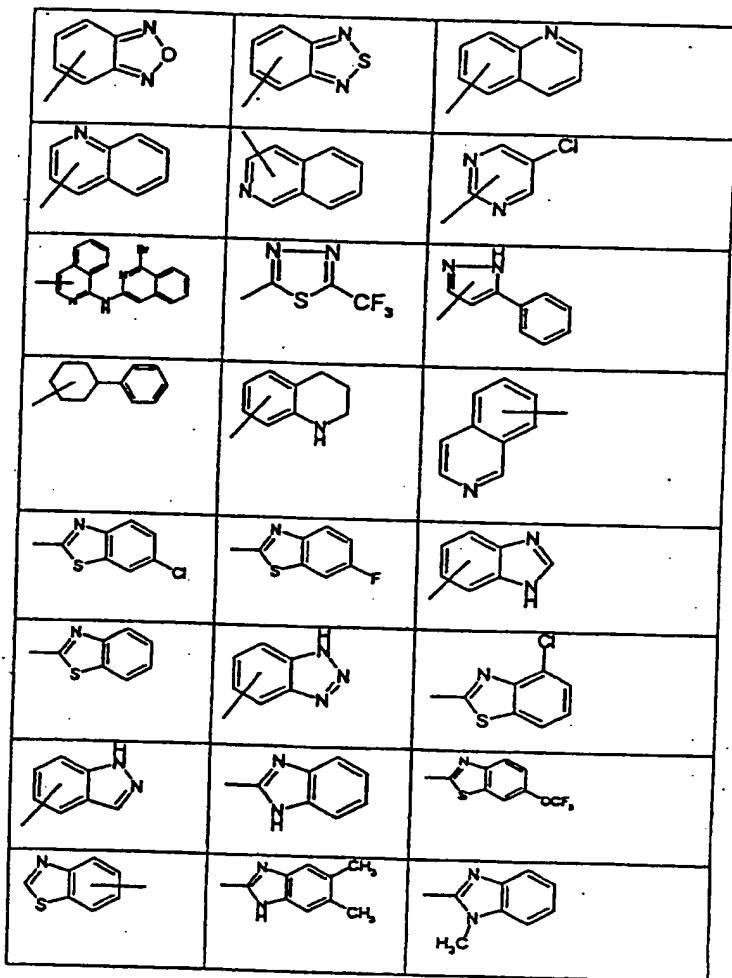
or A, Z and R¹ together form the group



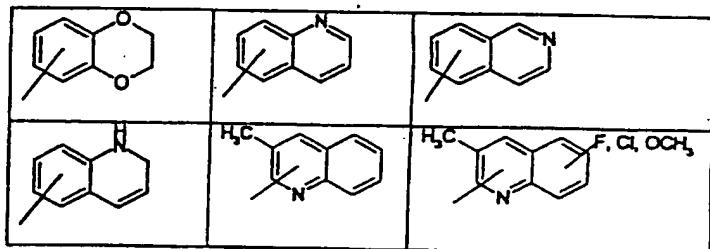
m, n, and o stand for 0-3,
q stands for 1-6,
R_a, R_b, R_c, R_d, R_e and R_f, independently of one another, stand for hydrogen, C₁₋₄ alkyl or the group =NR¹⁰,
X stands for the group =NR⁹,
Y stands for the group -(CH₂)_p,
P stands for 1-4,
R¹ stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C_{1-C₄} alkyl, C_{1-C₄}

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C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group

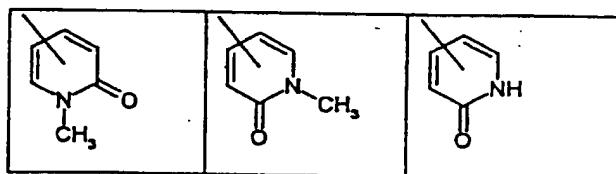


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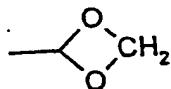
whereby phenyl, substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A

R^2 stands for hydrogen or C_{1-6} alkyl,
 R^3 stands for naphthyl, biphenyl, phenyl,
thiophenyl, furanyl, oxazolyl,
thiazolyl, imidazolyl, pyrazolyl,
pyridyl, pyrimidinyl, triazinyl,
quinolinyl or isoquinolinyl that is
unsubstituted or that is optionally
substituted in one or more places with
halogen, C_{1-6} alkyl, C_{1-6} alkoxy or
hydroxy, or for the group



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R^4 , R^5 , R^6 and R^7 , independently of one another, stand for hydrogen, halogen or C_{1-6} alkoxy or C_{1-6} alkyl that is unsubstituted or optionally substituted in one or more places with halogen, or R^5 and R^6 together form the group

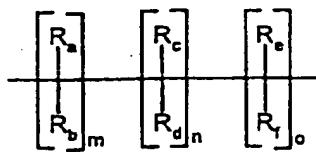


R^8 , R^9 and R^{10} , independently of one another, stand for hydrogen or C_{1-6} alkyl, as well as their isomers and salts, whereby, if W stands for oxygen, R^2 stands for hydrogen, R^9 stands for hydrogen, Y stands for the group $-(CH_2)_p$, in which $p = 1-4$, and R^1 stands for pyridyl, or

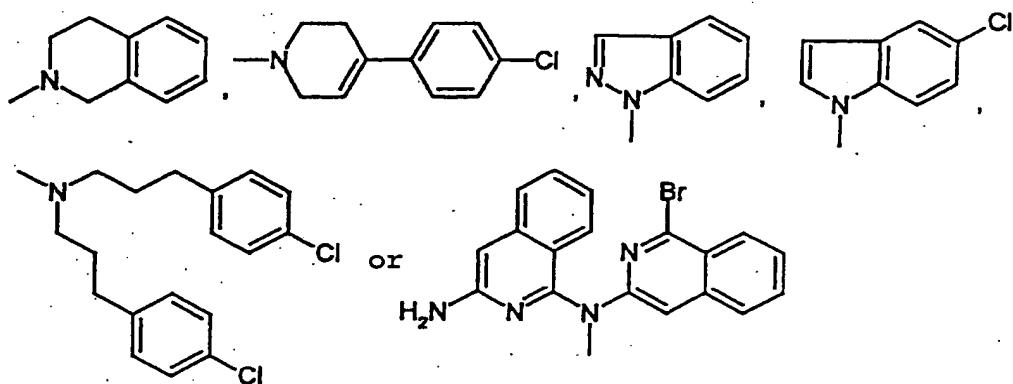
Y stands for the group $-(CH_2)_p$, in which $p = 1$, and R^1 stands for phenyl or phenyl that is substituted in one place by methyl, chlorine or bromine, and Z stands for methyl or ethyl, R^3 must not stand for pyridyl, phenyl or phenyl that is substituted in one place by methyl, chlorine or bromine.

3. Compounds of general formula I according to claims 1 and 2, in which

A	stands for the group $=NR^2$,
W	stands for oxygen, sulfur or two hydrogen atoms,
Z	stands for the group $=NR^{10}$, $=N-$, or $-N(R^{10})-(CH_2)_q-$ or the group

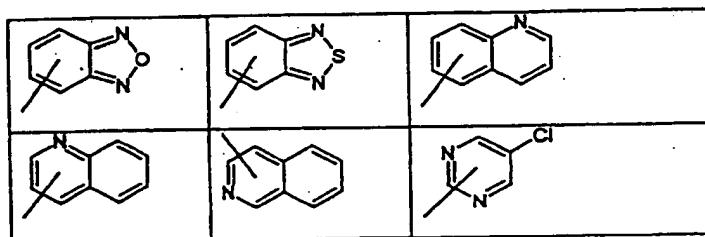


or A, Z and R¹ together form the group

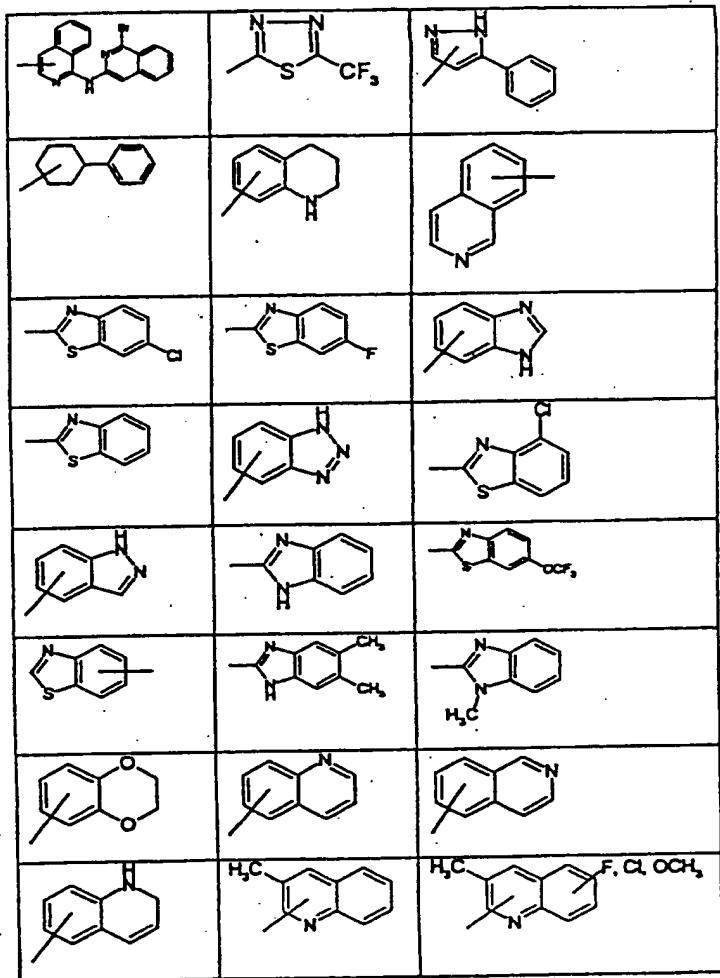


m, n and o stand for 0-3,
q stands for 1-6,
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group =NR¹⁰,
X stands for the group =NR⁹,
Y stands for the group -CH₂-,
R¹ stands for phenyl, pyridyl, p-chlorophenyl, p-methylphenyl, p-methoxyphenyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl,

thienyl, 6-fluoro-1H-indol-3-yl,
naphthyl, 1,2,3,4-tetrahydronaphthyl,
benzo-1,2,5-oxadiazole, 6,7-dimethoxy-
1,2,3,4-tetrahydro-2-naphthyl, or for
phenyl or pyridyl that is substituted in
one or more places with C₁-C₄ alkyl, C₁-
C₄ alkoxy, hydroxy, halogen, or
trifluoromethyl, or for the group



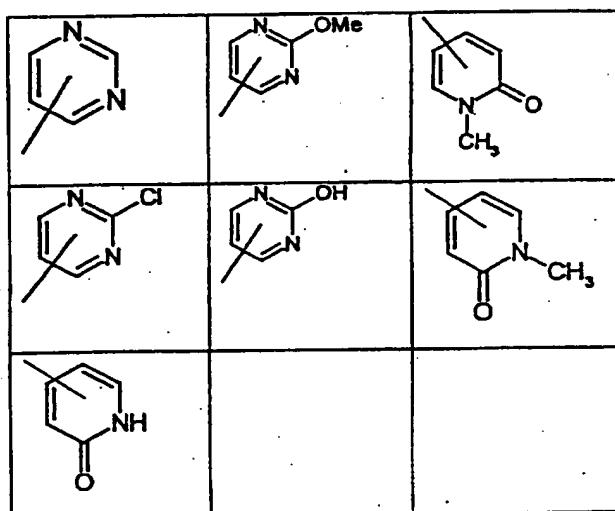
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whereby phenyl, or substituted phenyl or naphthyl is not right in the $=\text{NR}^2$ group in the meaning of A,
 R^2 stands for hydrogen or methyl,

R^3

stands for pyridyl or for phenyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group

 R^5 and R^6 ,

independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

 R^4 and R^7 ,

independently of one another, stand for hydrogen,

 R^9

stands for hydrogen,

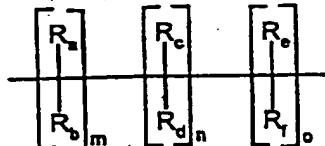
R^{10} stands for hydrogen or methyl,
as well as their isomers and salts, whereby if W stands for
oxygen, R^2 stands for hydrogen, R^9 stands for hydrogen,
 R^1 stands for pyridyl,

or

R^1 stands for phenyl or phenyl that is substituted in one
place by methyl, chlorine or bromine, and Z stands for methyl or
ethyl, R^3 must not stand for pyridyl or phenyl that is
substituted in one place by methyl, chlorine or bromine.

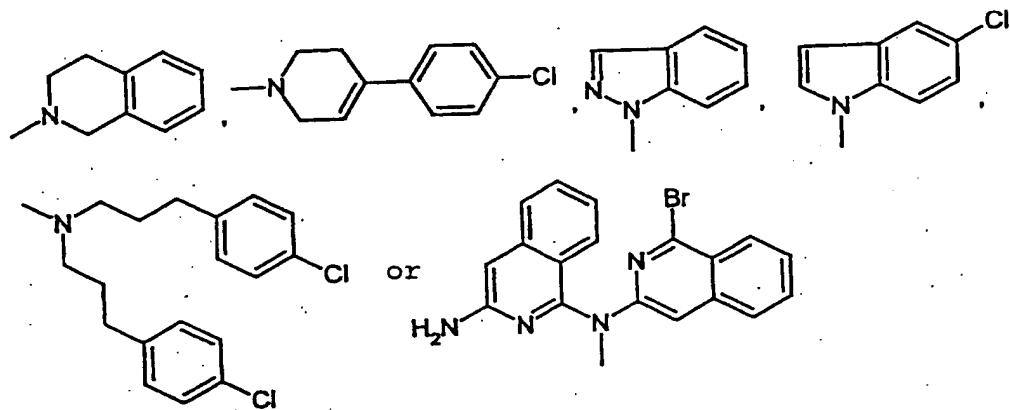
4. Compounds of general formula I according to claims 1 to
3, in which

A stands for the group $=NR^2$,
W stands for oxygen,
Z stands for the group $=NR^{10}$, $=N-$, or
 $-N(R^{10})-(CH_2)_q-$ or the group

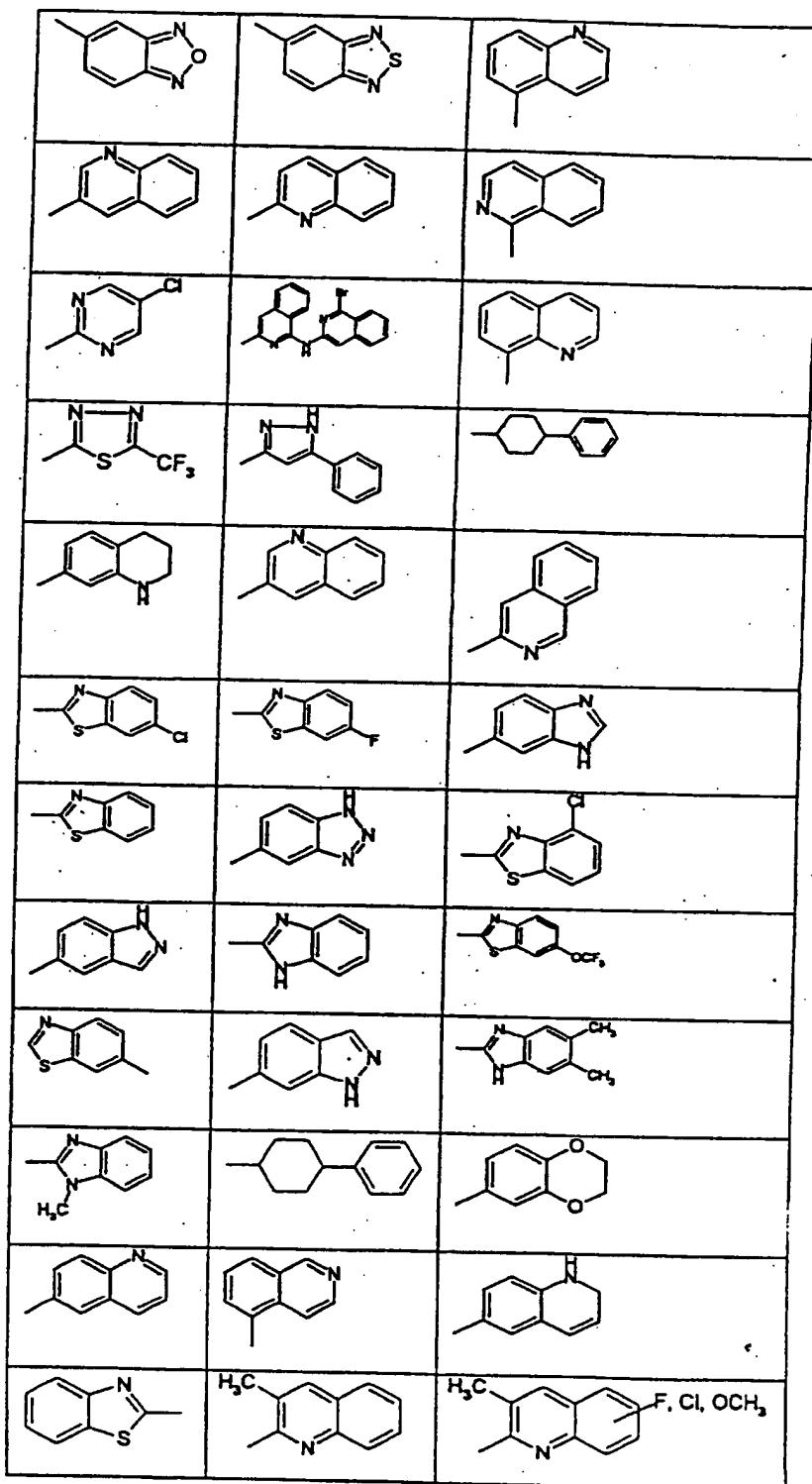


or A, Z and R^1 together form the group

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m , n and o stand for 0-3,
 q stands for 1-6,
 R_a , R_b , R_c , R_d , R_e , R_f , independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,
 X stands for the group $=NR^9$,
 Y stands for the group $-CH_2-$,
 R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group



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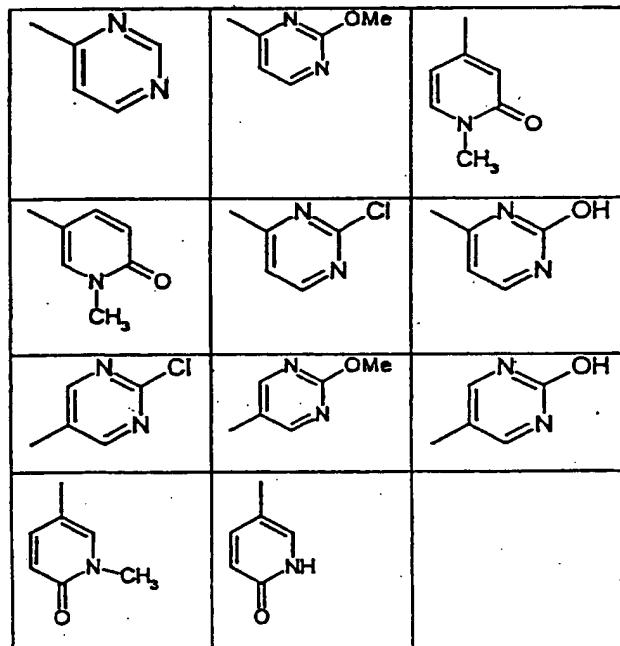
whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2

stands for hydrogen or methyl,

R^3

stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R⁵ and R⁶, independently of one another, stand for hydrogen, halogen, methyl, methoxy, or trifluoromethyl,

R⁴ and R⁷, independently of one another, stand for hydrogen and halogen,

R⁹ stands for hydrogen,

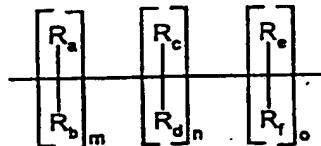
R¹⁰ stands for hydrogen or methyl,
as well as their isomers and salts, whereby if R² stands for hydrogen, R¹ stands for pyridyl,
or
R¹ stands for phenyl or phenyl that is substituted in one place by methyl, chlorine or bromine, and Z stands for methyl or ethyl, R³ must not stand for pyridyl or phenyl that is substituted in one place by methyl, chlorine or bromine.

5. Compounds of general formula I according to claims 1 to 3, in which

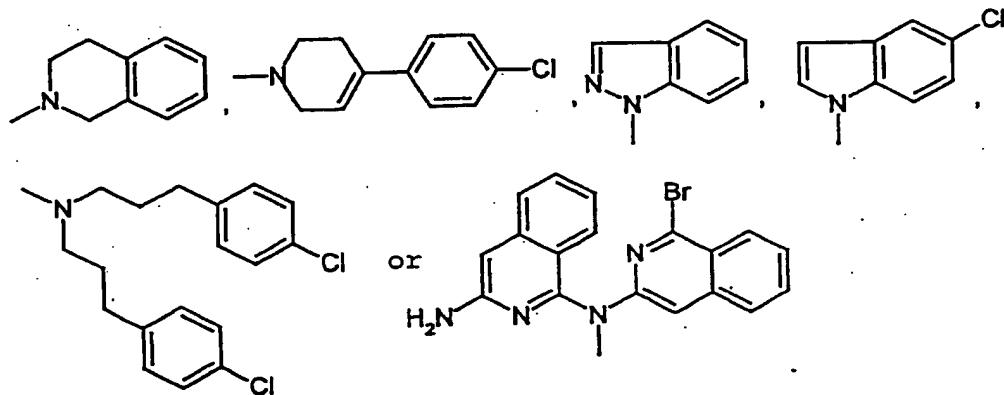
A stands for the group =NR²,

W stands for sulfur,

Z stands for the group $=NR^{10}$, $=N-$, $-N(R^{10})-$
 $(CH_2)_q-$ or the group



or A, Z and R¹ together form the group

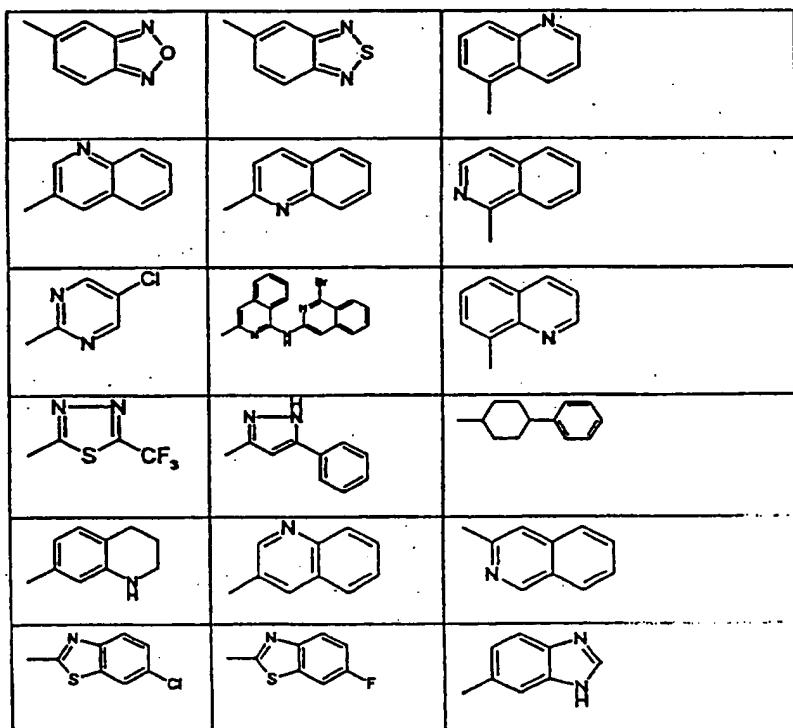


m, n and o stand for 0-3,
q stands for 1-6,
R_a, R_b, R_c, R_d, R_e, R_f, independently of one another, stand for hydrogen or methyl or the group =NR¹⁰,
x stands for the group =NR⁹,
y stands for the group -CH₂-.

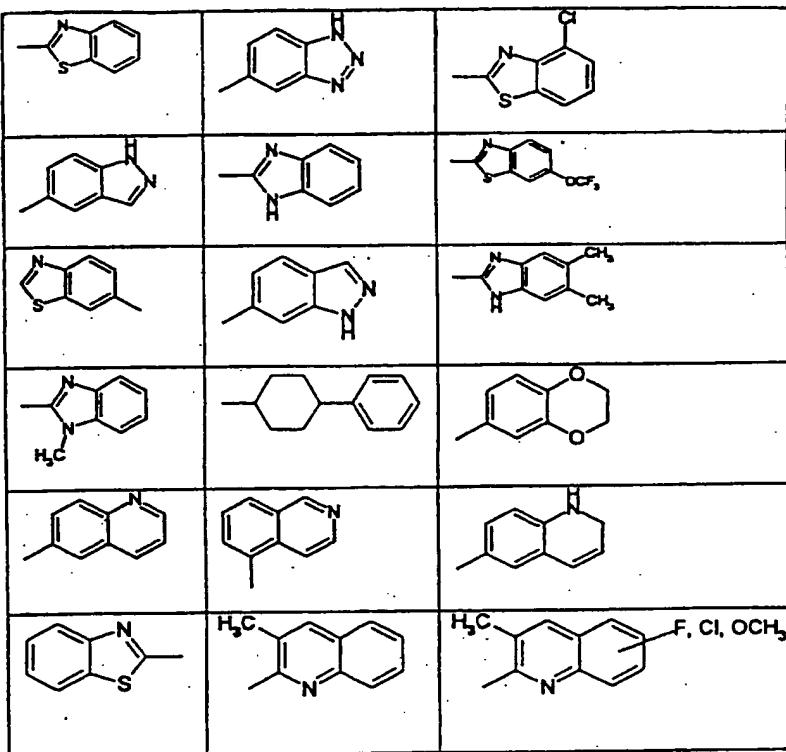
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R¹

stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for phenyl or pyridyl that is substituted in one or more places with C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group



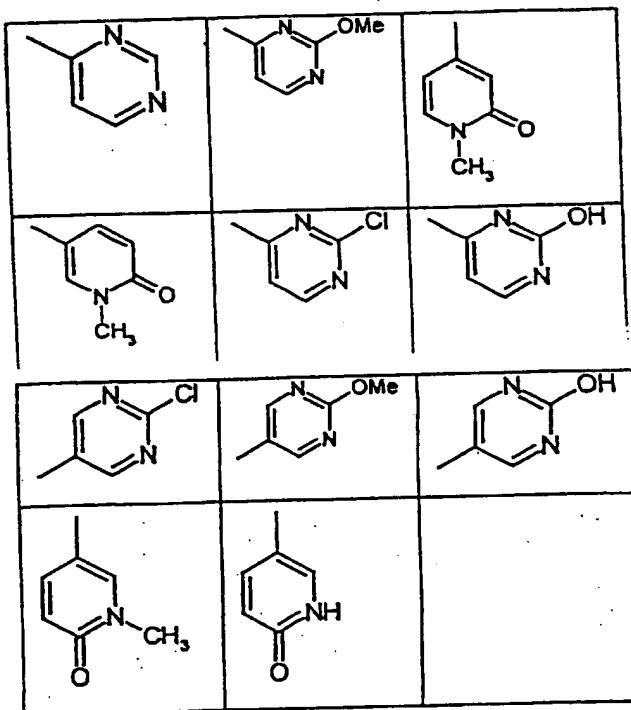
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whereby phenyl, or substituted phenyl or naphthyl is not right in the $=NR^2$ group in the meaning of A,

R^2 stands for hydrogen or methyl,

R^3 stands for pyridyl or for phenyl, pyridyl or 1,2,3,4-tetrahydronaphthyl that is substituted in one or more places with hydroxy, halogen, methyl or methoxy, or for the group



R^5 and R^6 , independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,

R^4 and R^7 , independently of one another, stand for hydrogen and halogen,

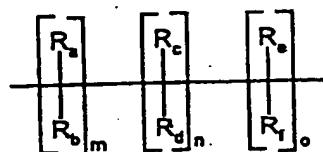
R^9 stands for hydrogen,

R^{10} stands for hydrogen or methyl,

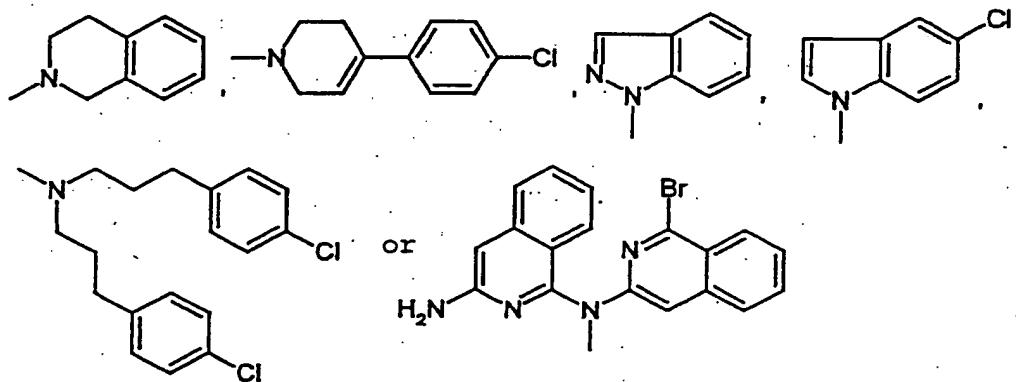
as well as their isomers and salts.

6. Compounds of general formula I according to claims 1 to 3, in which

A stands for the group $=NR^2$,
 W stands for two hydrogen atoms,
 Z stands for the group $=NR^{10}$, $=N-$, or
 $-N(R^{10})-(CH_2)_q-$ or the group



or A, Z, and R¹ together form the group



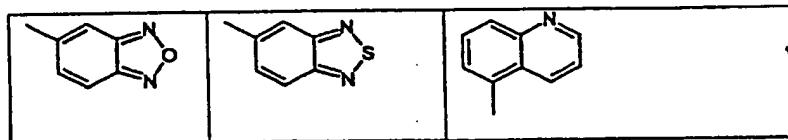
m, n and o stand for 0-3,
 q stands for 1-6,

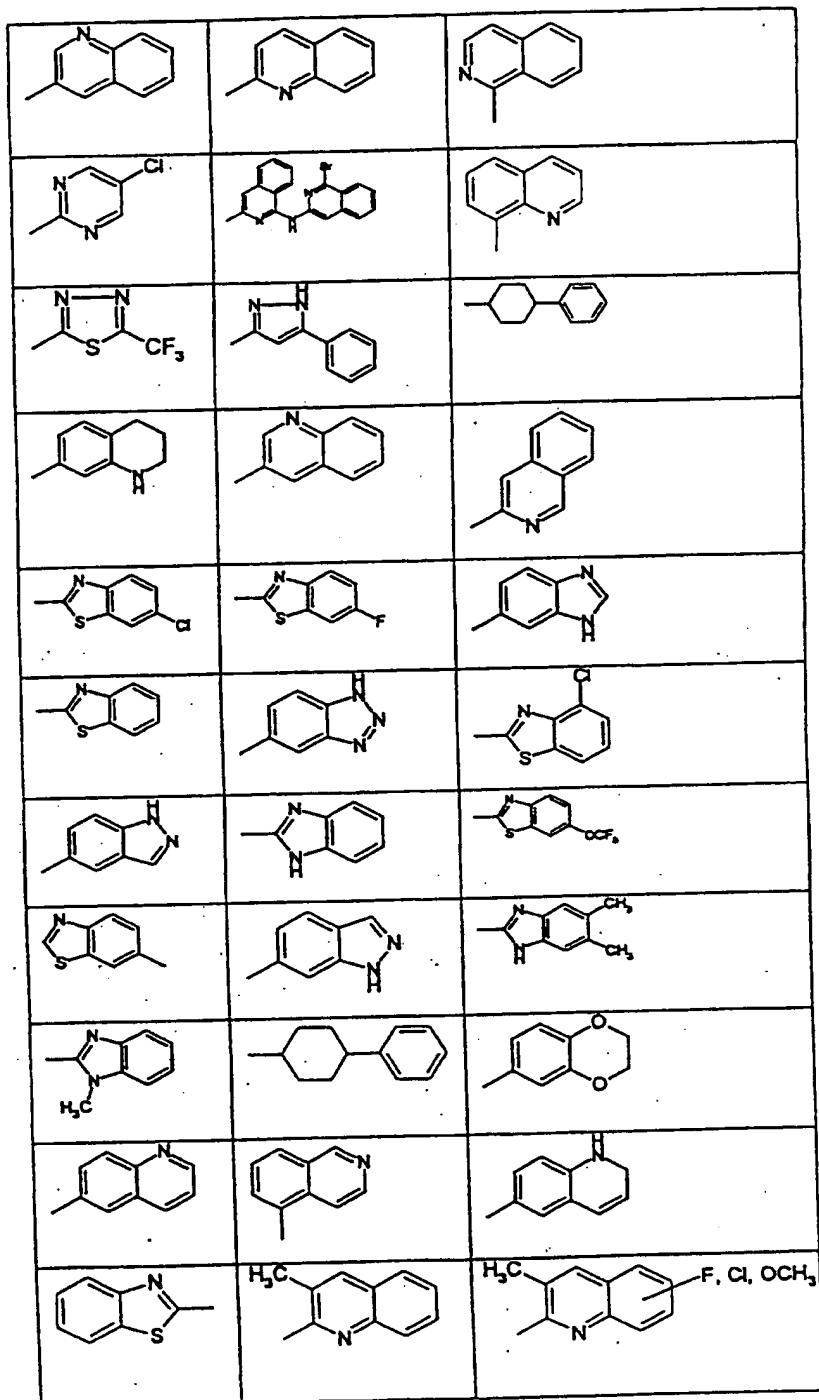
R_a , R_b , R_c , R_d , R_e , R_f , independently of one another, stand for hydrogen or methyl or the group $=NR^{10}$,

X stands for the group $=NR^9$,

Y stands for the group $-CH_2-$,

R^1 stands for phenyl, pyridyl, 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, naphthyl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole or 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl or for a phenyl or pyridyl that is substituted in one or more places with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, halogen, or trifluoromethyl, or for the group





whereby phenyl, or substituted phenyl or naphthyl is not right in the $=\text{NR}^2$ group in the meaning of A,

R^2

stands for hydrogen or methyl,

R^3

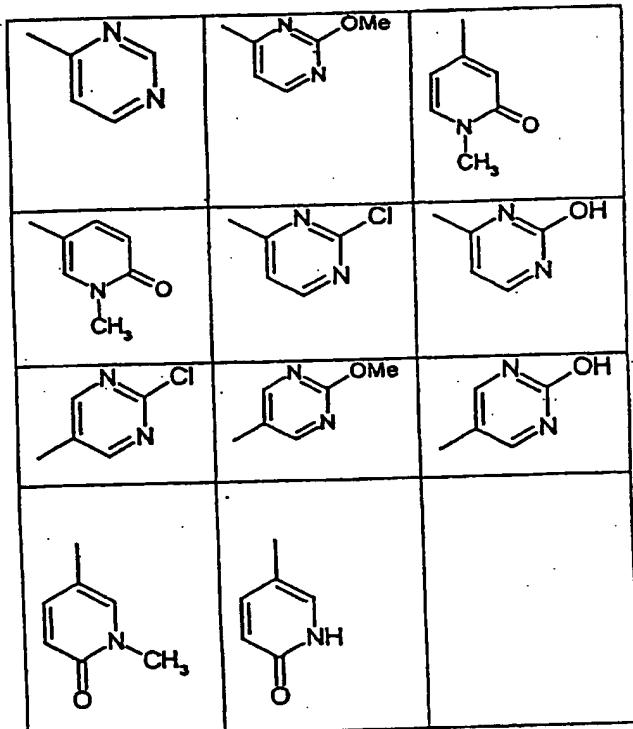
stands for pyridyl or for phenyl,

pyridyl or 1,2,3,4-tetrahydronaphthyl

that is substituted in one or more

places with hydroxy, halogen, methyl or

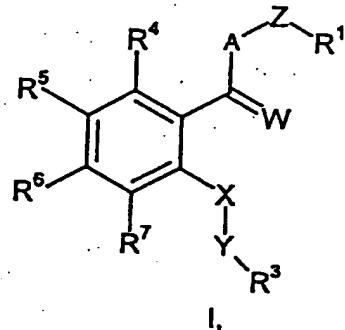
methoxy, or for the group



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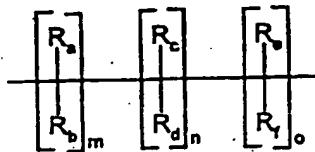
R⁴ and R⁷, independently of one another, stand for hydrogen, halogen, methyl, methoxy or trifluoromethyl,
 R⁵ and R⁶, independently of one another, stand for hydrogen and halogen,
 R⁹ stands for hydrogen,
 R¹⁰ stands for hydrogen or methyl,
 as well as their isomers and salts.

7. Use of the compounds of general formula I

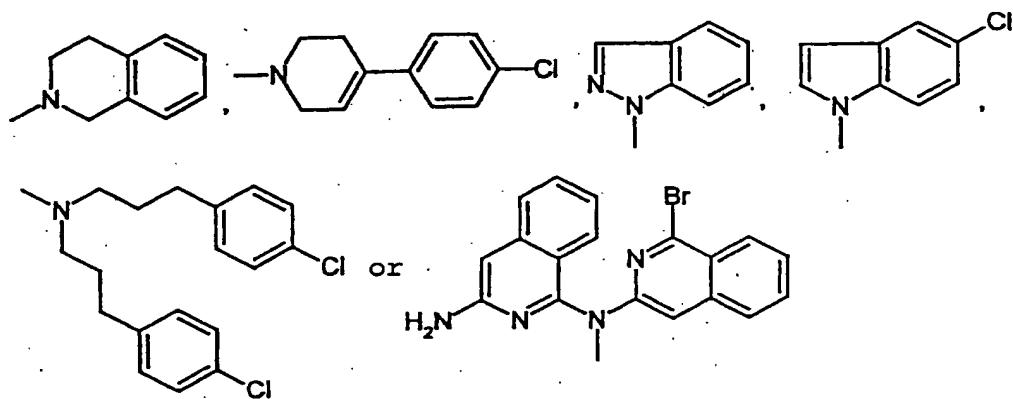


in which

A stands for the group =NR²,
 W stands for oxygen, sulfur, two hydrogen atoms or the group =NR⁸,
 Z stands for the group =NR¹⁰, =N- or -N(R¹⁰)-(CH₂)_q-, branched or unbranched C₁₋₆ alkyl or the group



or A, Z and R¹ together form the group



m, n, and o stand for 0-3,
q stands for 1-6,
R_a, R_b, R_c, R_d, R_e and R_f, independently of one another, stand for hydrogen, C₁₋₄ alkyl or the group =NR¹⁰, and/or R_a and/or R_b can form a bond with R_c and/or R_d or R_c can form a bond with R_e and/or R_f,
x stands for the group =NR⁹,

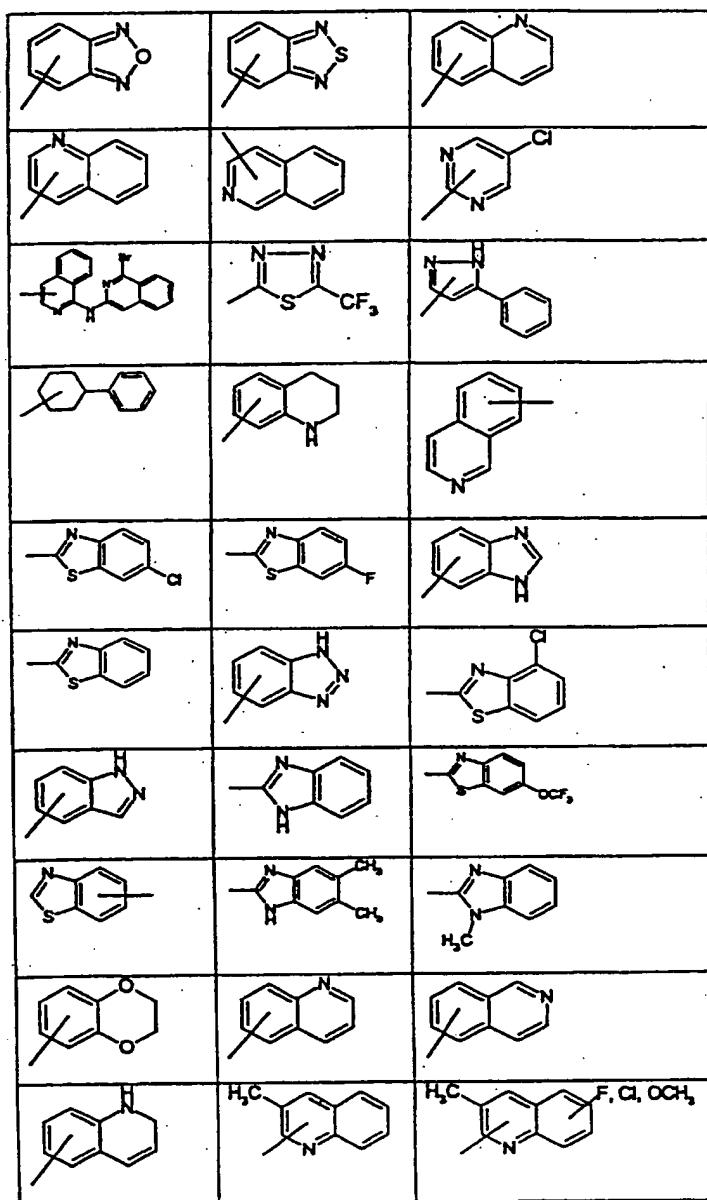
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y stands for the group $-(\text{CH}_2)_p-$,

p stands for 1-4,

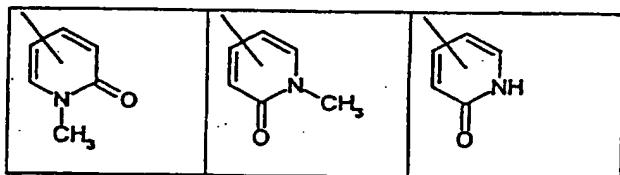
R¹ stands for C₁₋₆ alkyl that is unsubstituted or optionally substituted in one or more places with halogen, C₁₋₆ alkyl, C₁₋₄ alkoxy, hydroxy, nitro, cyano, or in one or more places with halogen, or C₁₋₆ alkoxy-substituted naphthyl, biphenyl, phenyl, thiophenyl, furanyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl or isoquinolinyl; or 5-chloro-2,3-dihydroindenyl, 2,3-dihydroindenyl, thienyl, 6-fluoro-1H-indol-3-yl, 1,2,3,4-tetrahydronaphthyl, benzo-1,2,5-oxadiazole, 6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthyl, or for the group

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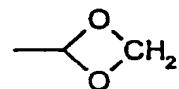


whereby phenyl, substituted phenyl or naphthyl is not right in the $=\text{NR}^2$ group in the meaning of A,

R^2 stands for hydrogen or C_{1-6} alkyl,
 R^3 stands for naphthyl, biphenyl, phenyl, thiophenyl, furanyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl or isoquinolinyl that is unsubstituted or that is optionally substituted in one or more places with halogen, C_{1-6} alkyl, C_{1-6} alkoxy or hydroxy, or for the group



R^4 , R^5 , R^6 and R^7 , independently of one another, stand for hydrogen, halogen or C_{1-6} alkoxy, C_{1-6} alkyl or C_{1-6} carboxylalkyl that is unsubstituted or optionally substituted in one or more places with halogen, or R^5 and R^6 together form the group



R^8 , R^9 and R^{10} , independently of one another, stand for hydrogen or C_{1-6} alkyl,

as well as their isomers and salts, for the production of a pharmaceutical agent for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

8. Pharmaceutical agent that contains at least one compound according to claims 1 to 6.

9. Pharmaceutical agent according to claim 8 for the treatment of tumors, psoriasis, arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases, such as cirrhosis of the liver, mesangial-cell-proliferative diseases, arteriosclerosis, injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter

treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents.

10. Compounds according to claims 1 to 6 and pharmaceutical agents according to claims 6 and 8 with suitable formulations and vehicles.

11. Use of the compounds of formula I according to claims 1 to 7 as inhibitors of tyrosine kinases KDR and FLT.

12. Use of the compounds of general formula I according to claims 1 to 6 in the form of a pharmaceutical preparation for enteral, parenteral and oral administration.

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